AMENDMENTS TO THE DRAWINGS

Please replace Figure 6A and 6B with the attached Drawing.

Attachments: Replacement Drawing

REMARKS

This Response, filed in reply to the Office Action dated June 11, 2007, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 13-15 are all the claims pending in the application. Claims 13-15 are rejected.

Objections to the Drawings

On page 2, the Office Action alleges that the 178bp band present in Figure 6A cannot be visualized.

Applicants attach a higher resolution copy of Figure 6 herewith, which Applicants believe fully complies with 37 CFR 1.121(d). Applicants respectfully submit that the revised drawing provided herewith overcomes the objection.

Objections to the Specification

On page 3, the Office Action objects to the specification because Figure 1 allegedly contains a sequence that is not listed in the sequence listing and therefore is not identified by a SEQ ID NO. Applicants hereby submit a revised sequence listing that includes SEQ ID NO: 23, comprising the entire DNA sequence disclosed in Figure 1, and amend the description of Figure 1 on page 6 of the originally filed specification accordingly. Applicants respectfully submit that the amendment to the specification and substitute sequence listing provided herewith overcomes the objection.

Claim Rejection - 35 U.S.C. § 102(b)

Claim 13 is rejected under 35 U.S.C. § 102(b) as being anticipated by Lockhart *et al.* (U.S. Patent 6,040,138).

The Office Action alleges that Lockhart *et al.* disclose the following: a) reverse transcription of a sample mRNA with a reverse transcriptase and a primer consisting of oligo dT and a sequence encoding the phage T7 promoter to provide single stranded DNA template; b) second DNA strand polymerization using a DNA polymerase; c) addition of T7 RNA polymerase and subsequent RNA transcription from the cDNA template; d) successive rounds of transcription from each single cDNA template to amplify RNA and; e) detection of the amplification products by hybridization to an array. The Office Action further alleges that Lockhart *et al.* disclose that the nucleic acids are labeled with fluorescent labels before hybridization, so that upon hybridization they can be detected.

Further still, the Office Action asserts that Lockhart *et al.* disclose a method wherein different and non overlapping portions of the selected DNA molecule are analyzed, because Lockhart *et al.* allegedly disclose that the method can be used to simultaneously monitor the expression of a multiplicity of genes.

The Office Action asserts that each gene is being interpreted as a different and non-overlapping portion of a selected DNA molecule and that, with regard to the instant claims, the repeating step of (C) can occur simultaneously with the step of (B). The Office Action asserts that "the claims are not limited to doing step (B) and then doing step (C); *but* rather the claims include doing steps (B) and (C) simultaneously."

Applicants respectfully submit that the claimed invention is not anticipated by Lockhart *et al.*, in view of the following remarks.

First, Claim 13, step (B)(i)(a) of the instant claims mandates "forming a RNA-DNA duplex comprising one of said RNA transcripts and a complementary DNA molecule adhered thereto, said duplex is formed by synthesizing a first strand DNA molecule complementary to at least a portion of one of said RNA transcripts using (1) said first oligonucleotide primer to prime synthesis of said first DNA molecule." Further, step (B)(i) of Claim 13 defines "said first oligonucleotide primer" as being "complementary to a sequence of at least 10 continuous nucleotides located at or near the 3'-end of said selected portion of said selected DNA molecule." Therefore, Claim 13 mandates that first strand cDNA synthesis must be initiated with an oligonucleotide primer that (1) binds to the RNA transcript and (2) contains a region that is complementary to at least 10 continuous nucleotides in said selected DNA molecule. In the portion of Lockhart *et al.* cited by the Examiner, first strand cDNA synthesis is not initiated using an oligonucleotide that contains a region that is complementary to at least 10 continuous nucleotides in said selected DNA molecule. Rather, Lockhart *et al.* use an oligo-dT primer that hybridizes to all mRNA molecules via complementary base-pairing with the stretch of 100-250 adenosine residues at the 3'-end of all mRNA molecules (i.e. the "poly-A tail"). It is common technical knowledge that the "poly-A tail" is added post-transcriptionally by a nuclear polyadenylate polymerase, and thus is not complementary to the DNA template. Therefore, the oligo-dT primer used by Lockhart *et al.* does not contain a region complementary to at least 10 continuous nucleotides in said selected DNA molecule. Accordingly, Lockhart *et al.* fails to teach an essential element of the claimed invention. Applicants respectfully submit that Claim 13 is not anticipated by Lockhart *et al.* at least for the foregoing reason.

Second, Lockhart *et al.* disclose that first strand cDNA synthesis is initiated from an mRNA transcript using a "primer consisting of oligo dT and a sequence encoding the phage T7

promoter to provide single stranded DNA template." Thus, not only do Lockhart *et al.* fail to teach how the RNA-cDNA duplex is converted to a single stranded DNA molecule, as is mandated by the instant claims (using ribonuclease H, Claim 13 (B)(i)(b)), but in the method of Lockhart *et al.*, the RNA transcriptable promoter is incorporated within the primer that mediates first strand cDNA synthesis (i.e. said first oligonucleotide primer). In contrast, instant Claim 13(B)(i)(c) mandates that "said second primer comprises an RNA-transcriptable promoter at its 5'-end." Again, Lockhart *et al.* does not teach an essential element of the claimed invention. The instant claims mandate that the primer used for DNA-DNA duplex formation contains an RNA-transcriptable promoter at its 5'-end. However, at best, Lockhart disclose the use of a primer used for RNA-cDNA duplex formation containing an RNA-transcriptable promoter sequence. Applicants respectfully submit that Claim 13 is not anticipated by Lockhart *et al.* at least for the foregoing reason.

Third, Lockhart *et al.* do not disclose step (B)(i)(e) of Claim 13. Lockhart *et al.* only disclose RNA amplification from a double-stranded cDNA template. Lockhart do not disclose that these progeny RNA molecules may be used for further RNA-cDNA duplex formation (i.e. further rounds of first strand synthesis). Thus, Lockhart *et al.* fail to teach another essential element of the claimed invention. Applicants respectfully submit that Claim 13 is not anticipated by Lockhart *et al.* at least for the foregoing reason.

Accordingly, withdrawal of the rejection is respectfully requested.

Claim Rejections - 35 U.S.C. § 103

Claims 14 and 15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lockhart *et al.* in view of Ishiguro *et al.* (*Nucleic Acids Research*, 1996, Vol. 24, No. 24).

The Office Action asserts that Lockhart *et al.* does not teach detection of the amplification product using an oligonucleotide probe labeled with an intercalating fluorescent dye, nor the use of an intercalating fluorescent dye that has a differential fluorescence characteristic depending on whether the probe exists in an unbound single-stranded state or in a bound duplex with the amplification product.

The Office Action alleges that Ishiguro *et al.* disclose a fluorescent intercalative dye-labeled probe which can recognize a specific nucleic acid sequence by linking a fluorescent intercalative dye as a label to a single-stranded oligonucleotide complementary in nucleic acid sequence to a specific nucleic acid sequence of the specific nucleic acid, so that when the single-stranded oligonucleotide hybridizes with the specific nucleic acid, the dye intercalates into the resulting double-stranded oligonucleotide to alter the fluorescent property.

The Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Lockhart *et al.* by using probes linked to fluorescent intercalative dyes as suggested by Ishiguro *et al.* According to the Office Action, using fluorescent intercalative dye-labeled probes for detecting nucleic acids was routinely performed in the art as demonstrated by Ishiguro *et al.* and thus one would have been motivated to use these probes since they enable detection and quantification of nucleotide specific hybrids, not just any double stranded hybrid.

In order to establish a *prima facie* case of obviousness, three criteria must be established. First, the references must, in combination, teach each and every limitation of the currently claimed invention, *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974). Second, sufficient reason must exist as to why one of skill in the art would combine the references to arrive at the claimed invention. Finally, there must be a reasonable expectation of success in combining the references, and this expectation of success must also be found in the references as well. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

As mentioned under the U.S.C. § 102(b) claim rejection, Lockhart *et al.* do not teach each and every element of the claimed invention. Applicants respectfully submit that the addition of Ishiguro *et al.* does not compensate for the deficiencies of Lockhart *et al.* since Ishiguro *et al.* only disclose the use of a fluorescently-labeled oligonucleotide. Therefore, Lockhart *et al.* and Ishiguro *et al.*, either taken alone or in combination, do not teach each and every element of the claims. Consequently, one of ordinary skill in the art would not have a reasonable expectation of success of arriving at the claimed invention by combining these two references.

Moreover, the method of Lockhart requires that a bound/free separation step, such as hybridization and removal of probe by washing, be employed (columns 21 and 27). However, Ishiguro *et al.* only disclose a detection method that does not use a bound/free separation step. Thus, as the nucleotide hybridization detection methods employed by Ishiguro *et al.* and Lockhart *et al.* are fundamentally different, one of ordinary skill in the art would have no reason to combine these references. In addition, Applicants respectfully disagree with the assertion of the Office Action that one would have been motivated to use the probes as disclosed by Ishiguro *et al.* since they would enable detection and quantification of nucleotide-specific hybrids, not just any double stranded hybrid. In column 23, lines 17-25, of Lockhart *et al.*, the use of labeled

target nucleic acids is disclosed. Moreover, on page 5 of the Office Action, it is alleged that Lockhart *et al.* discloses the labeling of target nucleic acids so that they can be detected upon hybridization. Therefore, one of ordinary skill in the art would have no reason to look to Ishiguro *et al.* in order to quantify nucleotide-specific hybrids when Lockhart *et al.* already discloses the use of labeled target nucleic acids that would allow such quantification.

Accordingly, Applicants respectfully submit that the claimed invention is not rendered obvious by the combination of Lockhart *et al.* and Ishiguro *et al.*

Accordingly, withdrawal of the rejection is respectfully requested.

Nonstatutory Obviousness-type Double Patenting

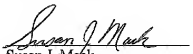
Claims 13-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-12 of copending Application No. 10/939,468, in view of Ishiguro *et al.*. The Examiner alleges that the present claims and the claims of Application No. 10/939,468 encompass methods for determining whether a selected DNA molecule encodes a gene expression region but that the present claims differ from the claims of Application No. 10/939,468 in that the present claims require the use of a probe linked to an intercalating dye.

Applicants assert that since Application No. 10/939,468 was abandoned on March 12, 2007, this rejection is moot.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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